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| <b>PRE-APPEAL BRIEF REQUEST FOR REVIEW</b>  |                                       | Docket Number (Optional)<br>9310-150 |
| CERTIFICATION OF ELECTRONIC TRANSMISSION<br><br>I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with 1.6(a)(4) to the U.S. Patent and Trademark Office on September 27, 2010.<br><br>Signature  | Application Number<br>10/537,562      | Filed<br>March 22, 2006              |
|   | First Named Inventor<br>Venema et al. |                                      |
| Typed or printed name<br>Gayle Endres   | Art Unit<br>1634                      | Examiner<br>Amanda Marie Shaw        |

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

applicant/inventor.  
 assignee of record of the entire interest.  
 See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.  
 (Form PTO/SB/96)  
 attorney or agent of record.  
 Registration number 57154  
 attorney or agent acting under 37 CFR 1.34.  
 Registration number if acting under 37 CFR 1.34 \_\_\_\_\_

  
Signature

Alice M. Bonnen  
Typed or printed name

919-854-1400  
Telephone number

September 27, 2010  
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.  
 Submit multiple forms if more than one signature is required, see below\*.

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| <input checked="" type="checkbox"/> | *Total of <u>1</u> forms are submitted. |
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This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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## REASONS FOR REQUEST FOR PRE-APPEAL BRIEF REVIEW CONFERENCE

This document is submitted in support of the pre-Appeal Brief Request for Review filed concurrently with a Notice of Appeal for U.S. Patent Application No. 11/372,586. Applicants hereby request a review of finally rejected claims 40, 44, 47 and 54, which stand rejected under 35 U.S.C. §102 as allegedly anticipated by Beckman et al. and finally rejected claims 41, 43, 48-50, 55, and 57-64, which stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beckman et al. in view of Majlessi et al. and Tsourkas et al. This request notes the clear error in facts and the absence of elements needed for a rejection of the pending claims under 35 U.S.C. §102 and under 35 U.S.C. §103(a). In particular, applicants submit that the Beckman et al. fails to disclose each and every element of the claimed invention, and alone or in combination, Beckman et al., Majlessi et al. and/or Tsourkas et al. fail to teach or suggest all of the recitations of the present claims, provide no motivation to combine the cited references and provide no reasonable expectation of success in achieving the presently claimed invention. Therefore, for these reasons, the Examiner has failed to establish the necessary requirements for an anticipation rejection under 35 U.S.C. §102 and has failed to present a *prima facie* case of obviousness under 35 U.S.C. §103(a).

The Examiner alleges that Beckman et al. teaches a MB probe comprising a stem with one or more unmodified nucleotides that can be in any position including in the 3' strand (March 30, 2010 Office Action, page 3). No support is provided for this allegation. The single disclosure in Beckman et al. regarding the location of any modified nucleotides in a MB is in a sentence in paragraph 0074, which states that "[f]or example, a MB comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5' end), or a MB can consist entirely of 2'-O-methyl nucleotides." While it is not clear which of the three 5' ends of the MB is being referred to in this sentence, i.e., the first or second arms (stems) or the loop, it is clear that the reference is to a 5' end and not a 3' end. One of skill in the art would not construe this sentence in Beckman et al. to be teaching that 2'-O-methyl nucleotide can be at any position including the 3' strand of the stem as alleged by the Examiner. In fact, until the March 30, 2010 Office Action, the Examiner has repeatedly argued that Beckman et al. teaches that the 2'-O-methyl nucleotide is found only in the 5' end of the MB probe (See, e.g., March 31, 2009 Office Action, page 3 and September 3, 2009 Office Action, page 3 and 9). The Examiner uses this interpretation of Beckman et al. to support the allegation that Beckman et al. discloses a base pair having only one modified nucleotide as claimed herein. According to the Examiner, the only modified nucleotide is in the 5' end of the MB and that modified nucleotide would allegedly necessarily have to pair with an unmodified nucleotide because the 3' end of the MB does not have modified nucleotides (*Id.*). The Examiner fails to reconcile this new interpretation of modified nucleotides in the 3' end with these earlier arguments.

An additional problem with this new interpretation of Beckman et al. is that Beckman et al. is trying to solve the problem of reducing the nuclease degradation (specifically 5' to 3' nuclease activity) of MB probes that are hybridized to a target nucleic acid (para 0042, 0043, 0074) and the solution provided is nuclease resistant MBs produced either by replacing unmodified nucleotides entirely with modified nucleotides or with only one or more modified nucleotides in the 5' end (para 0074). There is no teaching or suggestion of a modified nucleotide at the 3' end because the nuclease activity that Beckman et al. is concerned with relates to 5' to 3' nuclease activity and would not be blocked by a modified nucleotide in the 3' end of the stem. Thus, a MB of Beckman et al. having a modified nucleotide in the 3' end as suggested by the Examiner would not function for its intended purpose of being nuclease resistant. Therefore, one of skill in the art would read paragraph 0074 of Beckman et al. as disclosing, at most, MB probes comprised entirely of 2'-O-methyl nucleotides or having 2'-O-methyl nucleotides at the 5' end of the MB probe and nothing more. Accordingly, there is no disclosure in Beckman et al. of a modified nucleotide at the 3' end of the MB other than in a MB comprised entirely of modified nucleotides. Therefore, Beckman et al. fails to teach each and every limitation of claims 40, 44, 47, and 54 and as such fails to anticipate the presently claimed invention. Accordingly, Appellants respectfully request that this rejection be withdrawn.

Claims 41, 43, 48-50, 55 and 57-64 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beckman et al. in view of Majlessi et al. and Tourkas et al. The Examiner alleges that Beckman et al. teaches that MB probes can comprise one or more 2'-O-methyl nucleotides or can consist entirely of 2'-O-methyl nucleotides and cites to paragraph 0074 of Beckman et al. for support (March 30, 2010 Office Action, page 4). The Examiner then states that Beckman et al. does not teach the specifically claimed MB configurations (*Id.*). Instead, the Examiner relies upon Majlessi et al. and Tsourkas et al. as describing advantages of 2'-O-methyl nucleotide probes over 2'-deoxyoligonucleotide probes. On the basis of these disclosures, the Examiner concludes that it would be routine experimentation to design probes which are equivalents to those being claimed. Appellants disagree.

As discussed above, Beckman et al. fails to teach or suggest a MB probe having modified nucleotides in the 3' strand of the stem of the probe as claimed in the present invention. Beckman et al. further fails to teach or suggest a MB probe comprising a stem having no base pair with more than one modified nucleotide and only one base pair with no modified nucleotide or a stem wherein each base pair comprises no more than one 2'-O-methyl nucleotides and only one base pair of the stem comprises no modified nucleotides or a stem wherein each strand of the stem comprises at least one

modified nucleotide and each base pair of the stem comprises no more than one 2'-O-methyl nucleotide as claimed in the present invention.

The secondary references, Majlessi et al. and Tsourkas et al., both describes the advantages of probes made entirely of modified nucleotides as compared to probes made entirely of unmodified nucleotides. These references, alone or in combination with Beckman et al., provide no guidance to one of ordinary skill in the art to specifically select the MB probes as claimed herein. Majlessi et al. does not teach MB probes but rather teaches linear probes comprised entirely of 2'-O-methyl nucleotides. Majlessi et al. describes the advantages of these linear probes only in relationship to the binding of the probe to the target DNA/RNA. Thus, the higher  $T_{ms}$ , affinities, and hybridization kinetics are related only to hybridization of the probes to the target nucleic acid and not to hybridization between two strands (5' and 3' ends) of MB probes.

Similar to Majlessi et al., Tsourkas et al. also describes the advantages of probes comprised entirely of 2'-O-methyl nucleotides as compared with probes comprised entirely of 2'-deoxynucleotides. Tsourkas et al. discloses that the stem-loop structure of a MB probe comprised entirely of 2'-O-methyl nucleotides is more stable than a MB probe comprised entirely of 2'-deoxynucleotides (page 5169, first full paragraph and page 5170, second column, first full paragraph). This greater stability of the stem-loop structure is taught by Tsourkas et al. to be the result of the 2'-O-methyl/2'-O-methyl interactions (Tsourkas et al., page 5173, first column, last sentence). Thus, in order to achieve a stable MB probe as taught by Tsoukas et al., at least the stem of the MB probe must consist entirely of 2'-O-methyl nucleotides so that when the stem is hybridized to itself (forming the hairpin structure), 2'-O-methyl nucleotides are able to hybridize with other 2'-O-methyl nucleotides. Thus, not only does Tsourkas et al. fail to provide one of ordinary skill in the art any motivation to produce MB probes comprising both unmodified nucleotides and modified nucleotides, but by teaching that the stability of the MB probe is the result of the 2'-O-methyl/2'-O-methyl interactions, Tsourkas et al. teaches away from MB probes having 2'-O-methyl nucleotides hybridized only to unmodified nucleotides and/or at least one base pair of the stem comprising no modified nucleotides as claimed in the present invention.

It is noted that the Examiner has not provided any reasoned explanation as to how making the probes of the present invention would be routine experimentation other than to suggest that an ordinary artisan would have had more than a reasonable expectation of success in designing probes that have better stability and do not open spontaneously through the use of a computer program (March 30, 2010 Office Action, page 6). No specific computer program is identified and applicants are unaware of any computer program that was available at the time of the filing of the present invention

that would allow the ordinary skilled artisan to select MB probes having better stability and lower spontaneous opening with any predictability or reasonable expectation of success. As stated in the recently published Guidelines Update "[s]imply stating the principle ...without providing an explanation of its applicability to the facts of the case at hand is generally not sufficient to establish a *prima facie* case of obviousness" (*Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex*, Federal Register 75, 53643-53660, 53645 (September 1, 2010)) (hereinafter "the Guidelines Update"). The Examiner has erred in failing to provide a reasoned explanation of how routine experimentation could be used by one of skill in the art to design the probes of the present invention based solely on the limited disclosures of the cited references.

Prior to Appellants' invention, the ordinary skilled artisan would have to have chosen from an extremely large number of possible configurations for MBs in order to identify any particular MB that would solve the problem of stability and spontaneous opening. Beckman et al. discloses MBs comprised entirely of modified nucleotides or comprised of one or more modified nucleotides in the 5' end of the MB; however, as conceded by the Examiner, Beckman et al. fails to disclose the specific MBs as claimed in the present invention. The secondary references only discuss the advantages of probes (MBs and linear) that are comprised entirely of modified nucleotides over those that are comprised entirely of unmodified nucleotides. Simply disclosing the advantages of MBs comprised entirely of modified nucleotides does not provide the guidance one of ordinary skill in the art would need in order to have a reasonable expectation of achieving the presently claimed invention. Based on what was known at the time the present application was filed, one of ordinary skill in the art would not have been able to predict which of the many possible MBs would have greater stability and lower spontaneous opening and consequently, would have had no reasonable expectation of success in achieving the presently claimed invention.

Further, contrary to Examiner's contention that designing probes which are equivalents to those being claimed would be routine experimentation, Appellants have unexpectedly discovered that the designing of a MB probe that has better stability and that does not open spontaneously, depends both on the presence and position of the nucleotide analogues in the stem and whether the nucleotide analogues are base-paired with other nucleotide analogues or with unmodified nucleotides. See, for example, Table 6 of Example 4 of the present specification, which shows that the use of MB probes consisting entirely of base pairs having only one type of nucleotide (unmodified or 2'-O-methyl nucleotides) results in high levels of spontaneous opening of the probe. Notably, the MB4 probe having all modified nucleotides has a greater percentage of spontaneous opening (IBL-Increase of Baseline) than Reference MB, which is comprised entirely of unmodified nucleotides. The MB4 probe

also has a greater percentage of spontaneous opening as compared to MB probes comprising a combination of unmodified and modified nucleotides. MB probes having 2'-O-methyl nucleotides base-paired with unmodified nucleotides also show increased stability, which is surprising in view of what was known in the art at the time the present invention was made. See Tsourkas et al., page 5173, first column, last sentence (teaching that the greater stability of the stem-loop structure of the MB probes is the result of the 2'-O-methyl/2'-O-methyl interactions). Furthermore, as demonstrated with probes MB8 and MB9 (Figures 17 and 18, respectively), having one base pair in the stem of the MB that is comprised of unmodified nucleotides, results in an unexpectedly low level of spontaneous opening as compared with probes not having such structure (see, Example 4, Table 6, and Figures 17 and 18). None of the cited art teaches or suggests that the content and placement of the modified nucleotides in a MB probe with respect to unmodified nucleotides could or would play a role in the functional features of a MB probe. Due to such deficiencies in their teachings, none of the cited references provide one of ordinary skill in the art any motivation to produce the MB probes of the present invention or any reasonable expectation of success in achieving the presently claimed invention. Without the guidance of the disclosure of the present invention, achieving the claimed MBs could not have been the result routine experimentation, as asserted by the Examiner.

Accordingly, in view of the foregoing, Appellants respectfully submit that Beckman et al., Majlessi et al. and Tourkas et al., alone or in combination, fail to teach or suggest all of the elements of the presently claimed invention, fail to establish any motivation to combine these disclosures so as to produce the presently claimed invention and fail to provide any reasonable expectation of achieving the presently claimed invention. Therefore, Appellants respectfully request the withdrawal of this rejection.

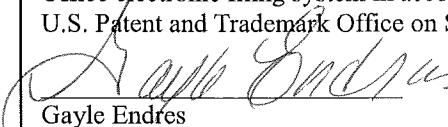
Respectfully submitted,



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**CERTIFICATION OF ELECTRONIC TRANSMISSION**  
I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on September 27, 2010.

  
Gayle Endres